



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2015

Two different manifestations of the same rare and lethal lung disease

Jäger, G ; Fontijn, J

Abstract: The first patient was born spontaneously at 40 4/7 weeks of gestation after an uneventful pregnancy. The mother was G1/P1, the family history was unremarkable and the parents were not related. Apgar scores were 5, 2, and 4, at 1, 5, and 10 minutes, respectively, and the arterial umbilical cord pH was 7.38.

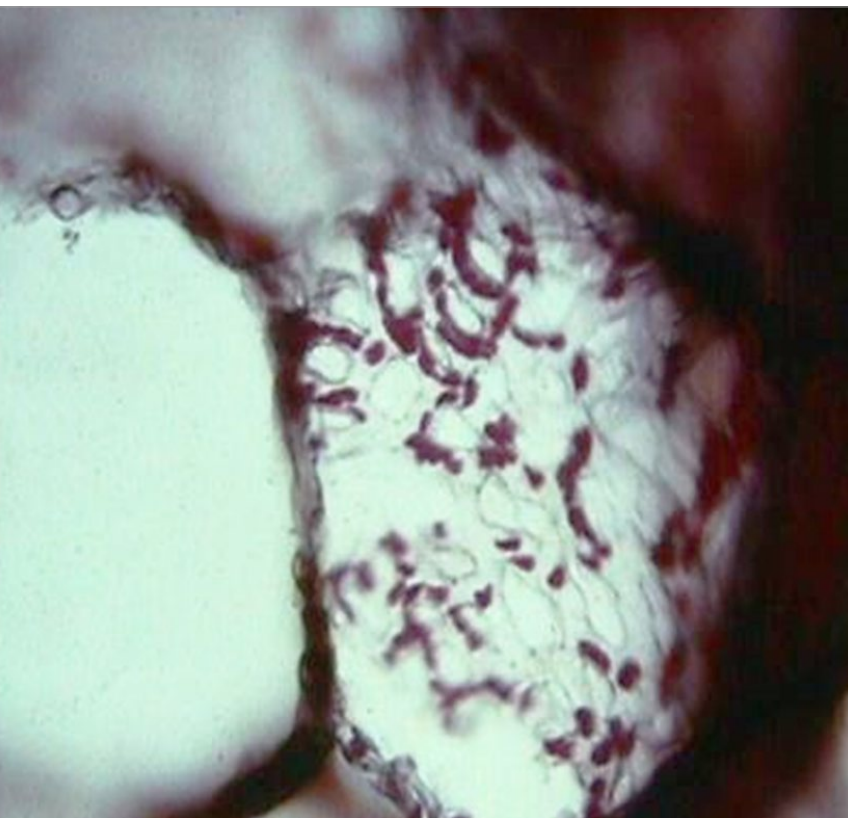
Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: <https://doi.org/10.5167/uzh-117850>
Scientific Publication in Electronic Form
Published Version

Originally published at:

Jäger, G; Fontijn, J (2015). Two different manifestations of the same rare and lethal lung disease.
<http://www.neonet.ch/en/>: Swiss Society of Neonatology.

Two different manifestations
of the same rare and lethal
lung disease

October 2015



Jäger G, Fontijn JR, Neonatal Intensive Care Unit,
Children's Hospital of Eastern Switzerland (JG),
Division of Neonatology, University Hospital Zurich (FJR),
Switzerland

Title figure:

Source: Prof. Thomas M. Berger (gift from Mary Ellen
Avery).

The first patient was born spontaneously at 40 4/7 weeks of gestation after an uneventful pregnancy. The mother was G1/P1, the family history was unremarkable and the parents were not related. Apgar scores were 5, 2, and 4, at 1, 5, and 10 minutes, respectively, and the arterial umbilical cord pH was 7.38.

Initially, the male infant seemed vigorous and cried, but very quickly showed signs of severe respiratory distress with retractions and hypoxia. In the first minutes of life, CPAP was initiated followed by assisted bag mask ventilation. Despite efforts to breathe and an FiO_2 of 1.0, there was no significant improvement and the oxygen saturation remained around 60–65%. A blood gas analysis at the age of 30 minutes showed severe mixed acidosis with a pH of 6.86, pCO_2 of 15 kPa, a BE of -23 mmol/l and a lactate of 13 mmol/l. The child was intubated and mechanically ventilated with high inspiratory pressures and 100% oxygen. Nevertheless, the boy remained hypoxic with saturations below 65%. Clinically, there were no signs of pneumothorax or congenital heart disease to explain the severe hypoxemia.

In order to be able to perform diagnostic evaluations (X-ray and echocardiography), the boy was transferred to the neonatal intensive care unit (NICU). On the way to the NICU, the oxygen saturation deteriorated further and the infant became bradycardic. Cardio-pulmonary resuscitation was started but was not successful and

was stopped after 20 minutes at the postnatal age of 2 hours. The blood gas analysis at that time revealed severe mixed acidosis with a pH of 6.5 and a lactate of 21 mmol/l. During resuscitation, a chest X-ray was obtained and showed bilateral pneumothoraces (Fig. 1). Echocardiography, performed during resuscitation, did not show any structural anomaly. At this time, the etiology of the severe respiratory failure remained unclear.

Finally, autopsy findings were compatible with a diagnosis alveolar capillary dysplasia (ACD) with immature lobular development indicating premature growth arrest, thickened alveolar septa and lymphangiectasis (Fig. 2 – 4).



Fig. 1

Chest X-ray obtained during resuscitation: bilateral pneumothoraces.

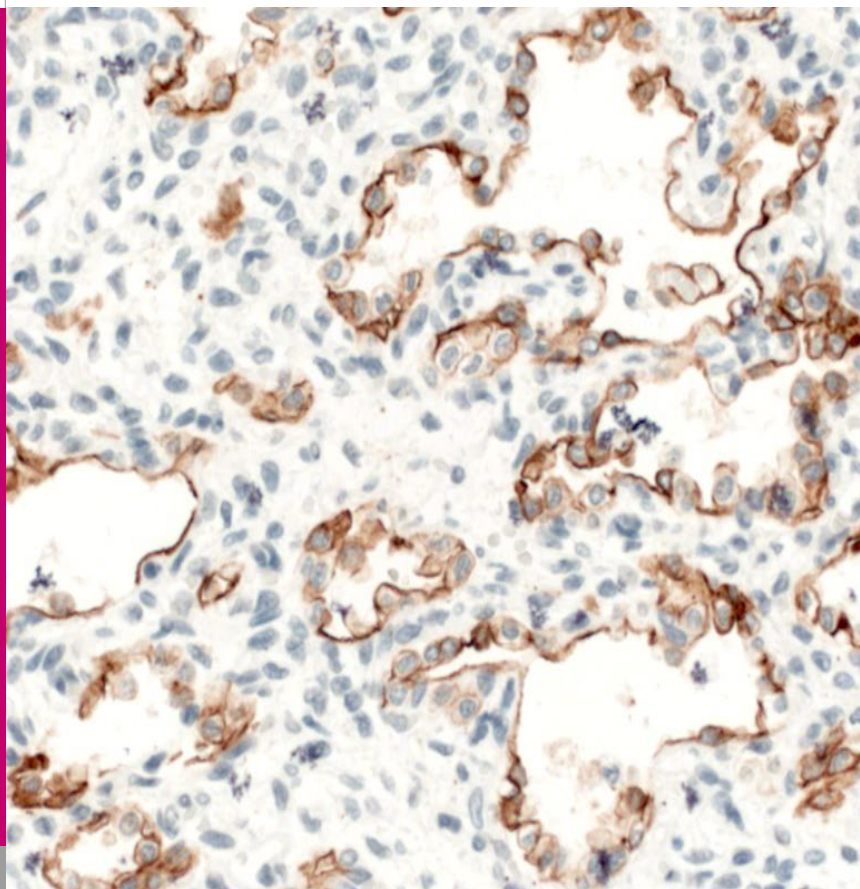


Fig. 2

Immunohistology with cytokeratin 7 staining of epithelial cells: immature lung structure with thickened septa (magnification x20).

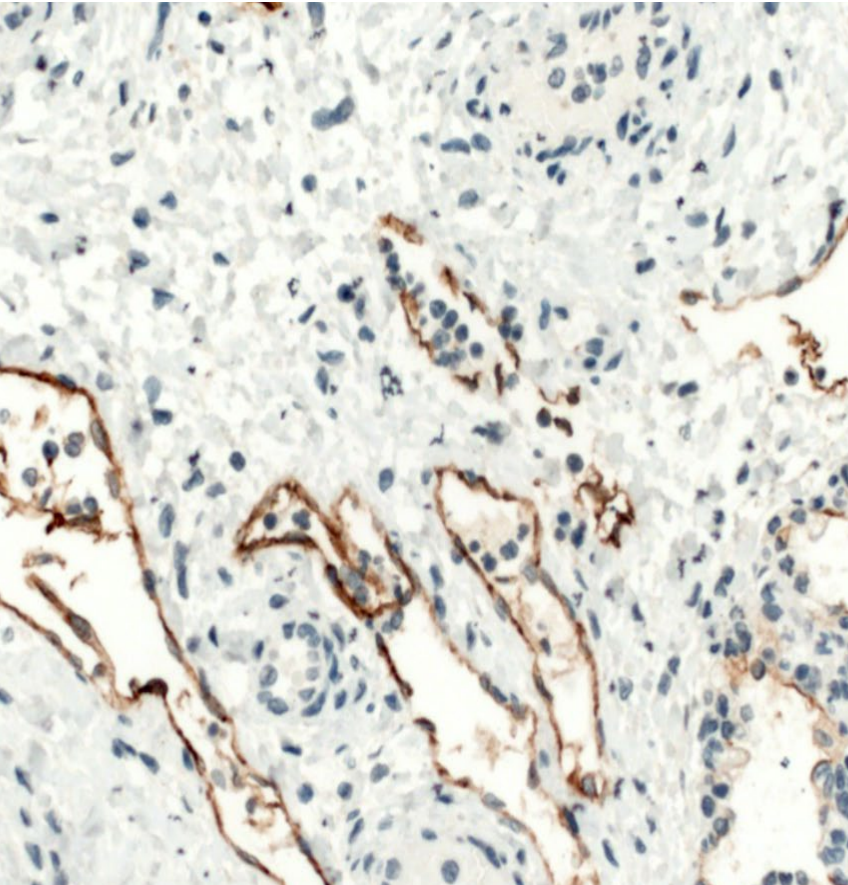


Fig. 3

Immunohistology with D2-40 staining of lymphatic endothelial cells: evidence of subpleural lymphangiectasia.

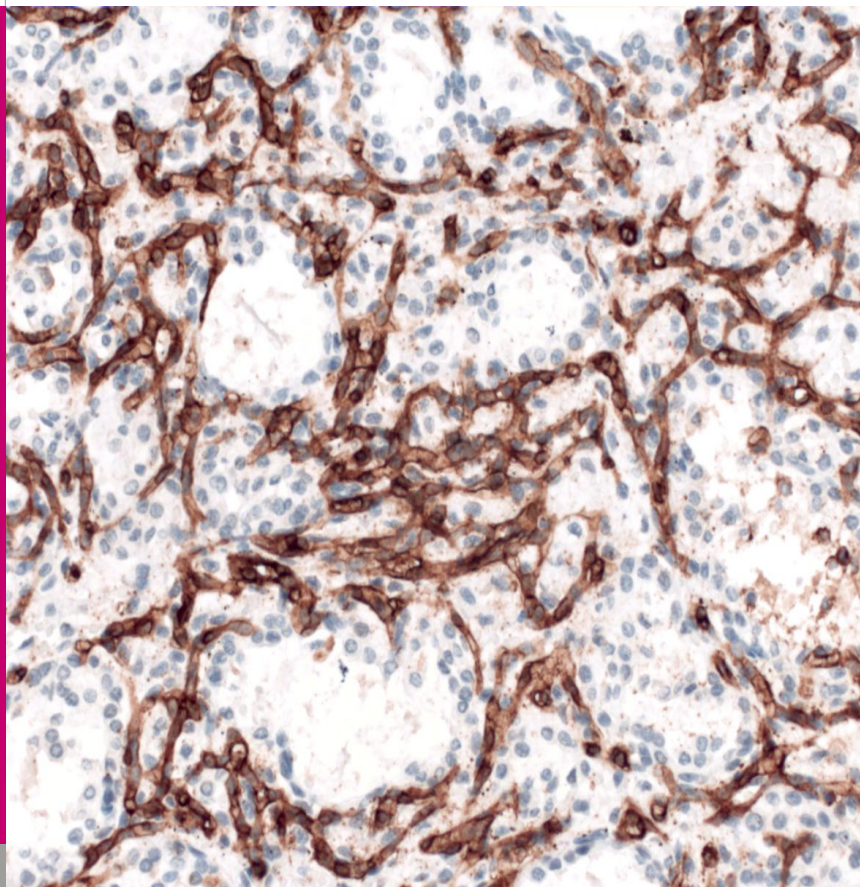


Fig. 4

Immunohistology with CD31 staining vascular endothelial cells: reduced capillary bed (magnification x20).

The second patient was a premature boy born at 31 4/7 weeks of gestation to a 34-year-old healthy G3/P2. The family history was unremarkable and the parents were not related. The pregnancy had been complicated by oligohydramnion, diagnosed at 21 6/7 weeks of gestation. Premature rupture of membranes had been excluded, and the kidneys had a normal appearance on ultrasound examination. When signs of intrauterine growth restriction and mild pleural effusions became apparent, amniocentesis was planned after induction of fetal lung maturation. When the mother was admitted to the hospital, a CTG was pathological and a Caesarean section was performed.

The male infant weighed 810 g (< P3), had a birth length of 33 cm (< P3), and a head circumference of 25 cm (< P3). Apgar scores were 3, 4, and 4 at 1, 5, and 10 minutes, respectively, and the umbilical artery pH was 7.27. Intubation and mechanical ventilation were necessary because of respiratory failure. Following these interventions, the boy could be oxygenated adequately with an FiO_2 of 0.5.

Physical examination showed multiple dysmorphic signs: large anterior and posterior fontanelles with distended sutures, low-set ears, asymmetrical palpebral fissures with suspected right-sided microphthalmia, micrognathia, a large curved nose, clinodactyly and ulnar deviation of both hands, cryptorchidism, hypospadias sine hypospadias and contractions of the larger joints.

After admission to the NICU, respiratory support had to be increased, surfactant was administered and a pleural drainage was placed because of a substantial pleural effusion on the right side. Clinically as well as echocardiographically, severe pulmonary hypertension was diagnosed in an otherwise anatomically normal heart. The kidneys were small and showed little corticomedullary differentiation. Diuresis was sparse during the first three postnatal days, but was then followed by polyuria. Renal function values were in the normal range.

Cerebral ultrasound showed periventricular flares and delayed gyration. A consultant in clinical genetics could not make a specific diagnosis. The further postnatal course was complicated by persistence and even aggravation of the pulmonary hypertension despite maximal supportive therapy. In addition, several metabolic derangements developed, such as severe conjugated hyperbilirubinemia without elevation of liver enzymes, hyperpigmentation of the skin and hypercalcemia (total calcium 3.1 mmol/l). The boy died following an episode of severe pulmonary hypertensive crisis on the 10th postnatal day.

Autopsy revealed ACD with malalignment of the pulmonary veins. In addition, there was an annular pancreas, adrenal hypoplasia and signs of severe asphyxia of the brain, liver and kidneys. The cholestasis was by exclusion felt to be explained by recurrent,

severe hypoxemia. Histological examination of the placenta showed a severe disturbed villous maturation, chronic villitis and lymphocytic deciduitis.

DISCUSSION

Severe hypoxia in a term neonate after birth is a difficult and challenging situation, especially when it occurs unexpectedly after an uneventful pregnancy as in our first case. In the second case presented, there were concerning findings during pregnancy, however, the final diagnosis of ACD could not be expected on the basis of these findings. In both cases, the final diagnosis was made by histopathology.

Alveolar capillary dysplasia (ACD) was first described in 1947 by Mac Mahon in a histopathological description (1). The key points, namely developmental abnormalities of the lungs and anomalies in other organs (i.e., septum defect of the heart, accessory spleen) were already mentioned at that time.

In 1981, a case of a neonate with severe, refractory hypoxemia and persistent pulmonary hypertension was described by Janney et al. Based on the histopathological findings, the term congenital ACD was coined (2). Since then, there have been around 100–200 descriptions in the literature, mostly single case presentations. It can be assumed that the number of cases is considerably higher, as the diagnosis is usually made histologically and only some of the patients with persistent pulmonary hypertension undergo autopsy or lung biopsy.

Nowadays, according to the Pediatric Interstitial Lung Disease Network Classification (3), the disease belongs

to the diffuse developmental disorders, resulting in a failure of fetal lung vascularization. Immature lobar development is typically characterized by a decreased number of pulmonary capillaries away from the alveolar epithelium (Fig. 4), thickened alveolar septae (Fig. 2), medial hypertrophy of small pulmonary arteries, malposition of the pulmonary vein branches in relation to the pulmonary arteries and lymphangiectasia (Fig. 3). For comparison, normal lung histology is shown in Fig. 5.

These histopathological findings (4, 5) are the key points to the diagnosis. There is no pathognomonic clinical or radiological finding for this disease. The typical clinical course is that of a severe hypoxemia with persistent pulmonary hypertension, which cannot be explained by radiographic abnormalities, cardiac disease or other conditions like asphyxia or infection. In nearly all cases, severe hypoxemia leads to persistent pulmonary hypertension refractory to therapeutic interventions.

There is a small number of patients described in literature with delayed manifestation of the pulmonary symptoms (5). These seem to be rare cases and belong to another spectrum of this disease. The cases, which manifest in the neonatal period, all have a severe, fatal course.

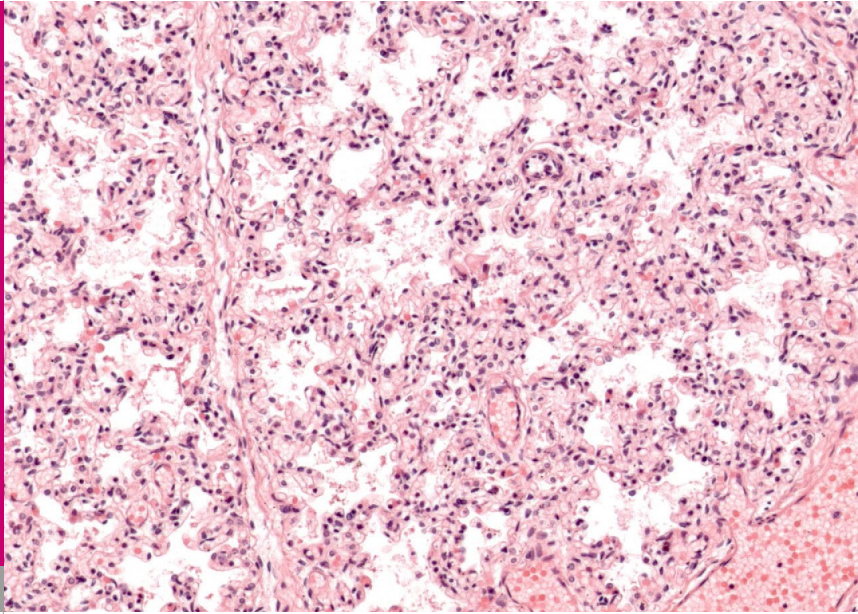


Fig. 5

HE stain: normal lung histology (magnification x10).

The fact that some neonates present with pulmonary symptoms only, and others (50–80%) present with symptoms in other organs as well is an interesting aspect. Manifestations of the cardiovascular, gastrointestinal or genitourinary system have been described, for example left ventricular hypoplasia, coarctation of the aorta, duodenal stenosis, aganglionosis, and esophageal atresia (4). In our second case, extra-pulmonary manifestations occurred in the gastrointestinal system and possibly the brain, although the latter were interpreted as consequences of severe asphyxia.

It must be emphasized that the main feature of this disease is a developmental disorder of the lung that is refractory to all forms of therapies (including NO, HFO and ECMO) and thus always lethal.

It is of paramount importance to make a diagnosis so parents can be counselled regarding possible consequences for future pregnancies. As mentioned above, diagnosis can only be made by autopsy or lung biopsy. Parents need to be informed and should give permission to perform at least a partial autopsy when ACD is suspected clinically.

According to literature, in about 40% of the cases, mutations or deletions in the FOXF1 factor gene have been described. There have been de novo mutations as well as autosomal dominant and recessive patterns (5, 6).

In conclusion, ACD is a rare and lethal pulmonary disorder. Most infants present with severe respiratory failure at birth, which often cannot be anticipated based on gestational age or the course of pregnancy. Even though the disorder is lethal, establishing the diagnosis will be helpful for both the parents and physicians involved in the care of such patients. After confirmation of the diagnosis, targeted genetic counselling is an option to answer questions regarding the risk of recurrence.

Acknowledgement

We would like to thank Dr. Christian Öhlschlegel, Institute of Pathology, St. Gallen, for the histopathological images.

1. Mac Mahon HE. Congenital alveolar dysplasia of the lungs. Am J Pathol 1948;24:919-931a (no abstract available)
2. Janney CG, Askin FB, Kuhn C. Congenital alveolar capillary dysplasia – an unusual cause of respiratory distress in the newborn. Am J Clin Pathol 1981;76:722-727 ([Abstract](#))
3. Dishop MK. Pediatric Interstitial Lung Disease: Classification and definitions. Pediatr Resp Rev 2011;12:230-237 ([Abstract](#))
4. Alameh J, Bachiri A, Devisme L, et al. Alveolar capillary dysplasia: a cause of persistent pulmonary hypertension of the newborn. Eur J Pediatr 2002;161:262-266 ([Abstract](#))
5. Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. Am J Respir Crit Care Med 2011;184:172-179 ([Abstract](#))
6. Sen P, Thakur N, Stockton DW, Langston C, Bejjani BA. Expanding the phenotype of alveolar capillary dysplasia. J Pediatr 2004;145:646-651 ([Abstract](#))

REFERENCES

SUPPORTED BY



CONTACT

Swiss Society of Neonatology

www.neonet.ch

webmaster@neonet.ch